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Evidence-based guidance on selected practice recommendations for contraceptive use: identification of research gaps☆

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1. Introduction

The Centers for Disease Control and Prevention (CDC) is developing the US Selected Practice Recommendations (US SPR) for Contraceptive Use, an adaptation of the World Health Organization's (WHO's) evidence-based SPR guidance addressing contraceptive management issues that, while common, may also be complex or controversial [1].

The recommendations in the US SPR will be based on the best available existing scientific evidence and expert guidance on such issues. The evidence was reviewed at an expert meeting held by the CDC in October 2011. In addition to informing development of recommendations for the US SPR, the meeting also served to identify research gaps for which additional evidence is needed to address or further clarify some common questions on contraceptive management and use. These research gaps are listed in Table 1, categorized by general area of interest. In this paper, we discuss three of the research gaps for purposes of illustration: (a) What are the most effective approaches to improve patient and provider understanding of and adherence to instructions for actions to take following dosing errors with oral contraceptive pills (OCPs) (missed pills), the transdermal contraceptive patch and the contraceptive ring? (b) What are the most effective and feasible approaches for prevention and management of bleeding irregularities among women using hormonal or intrauterine contraception? (c) What are the long-term effectiveness and safety of, and patient satisfaction with, hysteroscopic sterilization? For each of these questions, we discuss the significance of the issue, the type of evidence that is needed and the methodological challenges for conducting the needed research.

☆Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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2. What are the most effective approaches to improve patient and provider understanding of and adherence to instructions for actions to take following dosing errors with OCPs (missed pills), the transdermal contraceptive patch and the contraceptive ring?

Poor adherence to prescribed instructions for use of OCPs, the transdermal contraceptive patch and the contraceptive ring is common. Results of a 2004 population-based survey indicated that 28% to 58% of contraceptive pill users aged 18–44 years missed at least one pill in the 3 previous months [2]. A study of OCP users aged 18–31 years that used electronic monitoring devices for objective measurement of pill-taking behavior found that, on average, more than four active pills were missed per cycle [3]. While adherence has been shown to be better among users of the contraceptive patch than the pill, studies of the ring have yielded inconsistent results [4-6]. Poor adherence to these methods may lead to reduced protection against unintended pregnancy and increased likelihood of unscheduled bleeding; while such bleeding is not directly harmful to the woman, it may lead to discontinuation or complete cessation of use and thus a gap in contraceptive protection [7,8]. Due to the more frequent and self-administered dosing required for OCPs, patches and rings as compared with longer-acting methods, enhanced diligence is needed for correct and consistent use of these hormonal methods. Patient adherence to instructions is critical in the event of dosing errors (e.g., missed pills, delayed patch or ring replacement) to reduce the risk of unintended pregnancy.

A systematic review in this issue of *Contraception* examines evidence of the effect of missed combined hormonal contraceptives (CHCs) on contraceptive effectiveness and ovarian suppression [9]. Direct studies of the risk of unintended pregnancy following missed pills, forgotten ring removals or delayed patch replacement have not been conducted, but indirect evidence based on surrogate measures of pregnancy risk (e.g., ovulation and follicular development, progesterone levels) suggests that dosing errors that extend the hormone-free interval (HFI) are particularly risky. In addition, follicular activity appears to be greater when pill formulations of very low dose versus low dose are missed. While the extent to which the surrogate measures correspond to actual pregnancy risk is unclear, the combination of the studies examined by Zapata et al. [9], together with knowledge of the mechanisms of action of hormonal contraception, provides the best evidence available on which to base recommendations regarding how to manage dosing errors.

Many professional organizations provide instructions for actions to take following dosing errors [10-12]. In addition, guidance for what a woman can do if she misses combined or progestin-only contraceptive pills is provided in the WHO SPR [1]. Manufacturers also include instructions in patient package inserts (PPIs). However, the various instructions and guidance documents are often complex and sometimes conflicting. For example, recommendations for what to do after missed pills depend on the type of pill (e.g., progestin-only or combined oral contraceptive), the number of pills missed and the time in the cycle when pills are missed, and include guidance on when to take missed pills, when a new pack of pills should be initiated and hormone-free pills discarded, the need for alternative or

backup contraception and when to consider use of emergency contraception. Providers must familiarize themselves with the various sources of, and sometimes different, instructions available in order to select the guidance that best serves their needs and the needs of their patients.

Another systematic review in this issue of *Contraception* evaluates the evidence on patient understanding of missed pill instructions [13]. The studies summarized in the review utilized a variety of formats for presenting information to participants, including written information in PPIs, educational leaflets and brochures, as well as information presented through classroom instruction, counseling sessions and audiotaped educational sessions. Understanding of written instructions was found to vary widely and was weakest regarding what to do after two or more pills are missed as opposed to one pill. Overall, the evidence suggests that written instructions presented graphically and materials that present less as compared with more information are more easily understood by women. However, importantly, even among women who understand instructions about what to do when missing pills, intention to follow the instructions and adherence to the instructions do not necessarily follow [14]. While the studies examined in this systematic review represent the best evidence available, they had a number of methodological weaknesses, including enrollment of non-OC users who may have different motivation for understanding instructions about missed pills; lack of clarity as to whether participants recently read or referred to the instructions being evaluated and lack of baseline assessment of knowledge about what to do if pills were missed, both of which lead to uncertainty about any effect of the intervention on the outcome assessed; high attrition in studies involving follow-up and uncertain validity of survey instruments used to assess understanding of instructions. In addition, most of the studies only assessed the immediate impact of the materials being tested as opposed to the ability of women to either retain the information or to access and understand the information over time as method use continues. Finally, only four of the nine studies identified were conducted in the United States, of which two were of poor quality, with the remaining studies conducted in Western European countries and Jamaica. Although not a methodological weakness, results of such studies may not be generalizable to the United States.

Further research is needed to develop and evaluate innovative approaches that lead to improved understanding of and adherence to instructions when dosing errors occur among women who choose to use OCPs, the transdermal patch or the contraceptive ring. To address this research gap, good quality studies of US participants are needed that assess patient understanding of written, method-specific instructions regarding missed pills, patch or ring, and that go beyond this to identify and evaluate strategies that then lead to improved adherence to these instructions. From previous evidence [13], instructions that present the minimum amount of information needed to correctly inform the patient and those including a graphic component may be most likely to result in improved understanding. Strategies for ensuring that women have ready access to instructions also need to be evaluated, along with assessment of the effect of these strategies on changes in patient adherence over time. For example, are Web-based algorithms helpful, and do they improve adherence? What is the effect of printed charts and other graphic materials that can be referenced as needed?

Several challenges need to be considered in designing research to address this gap, including approaches to overcome the methodological weaknesses described above. Study designs that provide accurate measures of patient understanding of instructions and that minimize or can adjust for potential biases, such as randomized controlled trials, intervention studies and other designs that compare groups with and without the treatment or exposure of interest, will provide the best evidence. For studies assessing patient adherence to instructions, objective measures are needed to measure actual contraceptive use as opposed to relying on self-report which may result in overestimates. Possible approaches for more objective measures of pill-taking behavior include electronic monitoring devices that can detect when pill packs are opened or when pills are removed, and use of serum and urinary biomarkers to provide a measure of actual use [3,15,16]. Similar approaches could be used to obtain objective measures of patch and ring use. It will be important to determine whether patient understanding of and adherence to instructions vary by specific factors or patient characteristics. Such information is needed to guide intervention development and delivery. For example, adolescents have higher unintended pregnancy rates than adults, and the proportion of unintended pregnancies occurring while taking OCPs attributed to nonadherence has been found to be higher among adolescents (93%) than adults (86%) [17]. Compliance has also been found to be lower among adolescents than adults using the transdermal patch [18]. These results are consistent with studies showing nonadherence to be more common among adolescents than adults who use other types of long-term medications [19,20]. Hence, effective approaches for improving understanding of and adherence to instructions for dosing errors will likely differ between adolescents and adults. Additionally, recent studies document patient willingness to not follow instructions for use of contraception and other medications [14,21,22]. Qualitative research may be useful to obtain a better understanding of the reasons for this. Validated approaches are needed that can differentiate between nonadherence that is voluntary versus nonvoluntary; effects of strategies to improve understanding of missed pill instructions and adherence may differ depending on the reason for nonadherence, and different strategies for each may be needed.

Consideration needs to be given to the applicability and sustainability of approaches for actual use in practice. This will be particularly challenging for multicomponent intervention strategies, which, as has been suggested regarding adherence to hormonal contraception overall [23], may be more effective than single-component strategies. Optimally, studies of such strategies will be designed with sufficient power to allow evaluation of the various components.

Finally, the most beneficial strategies should ultimately lead to reductions in unintended pregnancy among users of OCPs, the patch and the ring, and may also lead to prevention of and reduction in dosing errors overall; long-term studies that are able to assess these outcomes would be especially useful.

3. What are the most effective and feasible approaches for prevention and management of bleeding irregularities among women using hormonal or intrauterine contraception?

Changes in menstrual bleeding patterns are common during use of progestin-only methods of contraception [e.g., progestin-only pills, depot medroxyprogesterone acetate (DMPA) injections, etonogestrel implant, levonorgestrel intrauterine device (IUD)], the copper (Cu)-IUD, and extended or continuous use of CHC. The most common changes vary by method, but include unscheduled spotting and bleeding, heavy or prolonged menstrual bleeding, oligomenorrhea and amenorrhea. These changes very rarely suggest a medical problem. Nonetheless, bleeding changes that occur during use of these methods are a primary reason for cessation of use [24,25].

A plethora of studies have been undertaken to determine if certain medications can help treat or prevent these bleeding irregularities. Many of these studies, however, lack sufficient numbers of subjects to be conclusive, and several of the studies tested contraceptive methods or treatment medications that are unavailable in the United States, limiting applicability to US-based practice. In a systematic review in this issue of *Contraception* that examines the evidence for treatments for heavy or prolonged menstrual bleeding related to the Cu-IUD [26], 16 studies of either poor or fair quality showed that prostaglandin inhibitors are the most widely studied therapeutic and prophylactic medications, and appear effective for reduction of bleeding associated with IUD use and may also prevent prolonged or heavy menstrual bleeding. While the review found some studies to indicate that antidiuretics and antifibrinolytic agents may be effective treatment, larger studies are needed to better assess their effectiveness as well as safety. Finally, despite study findings suggesting effectiveness of prostaglandin inhibitors for prevention or treatment of heavy or prolonged bleeding, good quality indirect evidence from one study found no effect of preventive treatment with a prostaglandin inhibitor on Cu-IUD continuation at 1 year [27]. This finding begs the question of why treat at all if treatment has no impact on method continuation.

Progestin-only contraceptive methods have been studied even more extensively than the Cu-IUD. In a 2007 Cochrane review of 23 randomized trials that examined medications for the treatment or prevention of bleeding irregularities with progestin-only contraceptives, some interventions, such as prostaglandin inhibitors, estrogen, tamoxifen and tranexamic acid, appeared to assist with cessation of bleeding, although the authors of the Cochrane review concluded that results did not support *routine* clinical use of any of the regimens included in the trials, particularly for long-term effect [28]. Prophylactic treatments were also reported in this review, although larger trials are needed to assess their effectiveness.

Another systematic review in this issue of *Contraception* examines the evidence regarding treatments for bleeding irregularities among women initiating extended or continuous CHC [29], with limited findings. Only three studies assessed possible treatments for an acute bleeding episode among new extended or continuous CHC users. One such study examined the effect of doxycycline, a matrix metalloproteinase (MMP) inhibitor, in an in vitro model

to test the hypothesis that this treatment might alleviate unscheduled bleeding caused from the up-regulation of MMPs; results were positive [30]. Despite the scientific plausibility, however, a randomized controlled trial found no benefit of doxycycline compared with placebo in treating an acute bleeding episode among COC extended users [31]. Two additional studies with more promising results used either a 3- or 4-day HFI as treatment of an acute bleeding episode among new continuous CHC users, demonstrating shorter bleeding episodes compared to users who did not take an HFI [32,33]. However, these two studies did not use a standardized bleeding scale, and although no pregnancies were reported, it was difficult to assess whether the HFI treatment recommendation would be followed accurately in a "typical" setting. As opposed to a research environment, in practice, under nonstudy settings, would women assume too many days for HFIs, thereby jeopardizing the effectiveness of their method?

The most successful strategy as it relates to positively affecting continuation of a method in the midst of bleeding irregularities may be structured anticipatory counseling; a research gap related to this was also identified (Table 1). The effectiveness of such counseling has been documented in several studies of DMPA users. In an open-label comparison trial of new users of DMPA, more women who had received structured counseling, as compared with those who received only routine counseling, chose to continue DMPA treatment through 1 year [34]. In a separate prospective observational study in Bolivia, researchers found that women using DMPA who received counseling about amenorrhea as a possible side effect and women who were told to return to the clinic for side effects had longer continuation of use than women who had not been given this counseling [35]. Similar findings were noted in a randomized trial of DMPA users in Mexico; women who received information about DMPA's mechanism of action and possible bleeding abnormalities at initiation and at each follow-up visit and who were encouraged to return to the clinic for concerns about the method had higher continuation rates at 1 year than users who received routine counseling [36].

The ultimate goal of identifying effective approaches for managing patients who experience bleeding irregularities while using contraception is to help women remain satisfied with their chosen method and to avoid interruptions in use or discontinuations that could place them at risk of unintended pregnancy. Studies of strategies to prevent and to treat bleeding irregularities are needed that have sufficient power to detect differences between treatment and placebo groups. More long-term follow-up studies are needed that follow participants for at least 6–12 months so that the effectiveness of treatment on both bleeding irregularities and on continuation of use can be assessed. Additionally, standardized definitions and approaches are needed to provide comparable baseline measures and measures of changes in bleeding patterns, such as reductions in blood loss and spotting. Treatment regimens to be tested need to be simple, cost-effective and easily accessible. Larger, multisite studies are also needed of medications that have been shown to be effective in smaller trials, such as Cox-2 inhibitors [37]. Finally, investigative efforts are needed to develop contraceptive methods that avoid or lead to only minimal bleeding irregularities in the first place. Improved cycle control has been shown with newer estrogen or progestin formulations in various CHC methods, but more research is needed for longer-acting methods [24,38].

Finding feasible solutions to bleeding irregularities associated with contraceptive use is not without its challenges. Because of the unpredictable nature of unscheduled bleeding, the feasibility of enrolling women into a study prior to or at the time of an acute bleeding episode is problematic. Standardization of definitions will require strong collaborative efforts among contraceptive researchers, and given that bleeding irregularities during contraceptive use affect women throughout the world, standardization on a global level would be most useful, yet much more challenging. It is also important to recognize that approaches for prevention or treatment found to be effective at one point in time may or may not be effective with newer methods, formulations or delivery systems as contraceptive technology evolves; a final challenge is the need to recognize this possibility and monitor effectiveness of accepted strategies as new contraceptive methods are developed.

4. What are the long-term effectiveness and safety of, and patient satisfaction with, hysteroscopic sterilization?

Female sterilization is a leading method of contraception in the United States, with more than 10 million women of reproductive age having been sterilized. Female sterilization, used by 16.7% of reproductive-aged US women using contraception, lags only slightly behind oral contraceptives, used by 17.3% of US women using contraception, as the most popular form of contraception [39]. In terms of surgical approach, female sterilization is performed by laparotomy, laparoscopy or hysteroscopy. Over the last few decades, fairly extensive information has accumulated on the safety and effectiveness of abdominal and laparoscopic approaches to female sterilization [40]. The largest, prospective study of female sterilization in the United States was the US Collaborative Review of Sterilization (CREST) which enrolled patients from 1978 to 1987. This study followed more than 10,000 sterilized women for up to 14 years to assess safety, effectiveness and other sequelae such as regret, sexual function, menstrual abnormalities and future risk of hysterectomy. Overall, CREST found that female sterilization was safe with low rates of intraoperative and postoperative complications [41]. Furthermore, there was no evidence of increased risk of later sequelae such as menstrual abnormalities or adverse effects on sexual function [42,43]. However, women who underwent tubal sterilization were at an increased risk of subsequent hysterectomy compared with age-matched women who were not sterilized [44]. Regret among sterilized women was not uncommon, particularly among younger women, with 20% of women sterilized under the age of 30 years later regretting their decision to be sterilized [45].

Although female sterilization is highly effective with very low long-term probability of pregnancy, a key finding from CREST was that pregnancies occurred as long as 10 years after the sterilization procedure with both abdominal and laparoscopic approaches [46]. Furthermore, with the introduction and integration of new methods of tubal sterilization, such as laparoscopic approaches, there was initially a “learning curve,” and failure rates declined over time. For example, the failure rates from laparoscopic bipolar coagulation were significantly higher in an earlier time period (1978–1982) compared with a later time period (1985–1987) [47].

In recent years, hysteroscopic approaches to female sterilization, which use hysteroscopy to access the fallopian tubes transcervically and place an occlusive material, have been developed and marketed. Although these methods seem to be growing in popularity, national estimates of the use of hysteroscopic sterilization are largely unavailable. National estimates of contraceptive method use in the United States are provided by the US National Survey of Family Growth which collects information on tubal sterilization but does not differentiate by surgical approach. Until recently, two hysteroscopic systems approved for use by the US Food and Drug Administration were available in the United States: however, one of these was voluntarily removed from the market by the manufacturer in April 2012.

Unlike other methods of tubal sterilization, hysteroscopic methods are not immediately effective, and patients must therefore use alternative contraception until bilateral tubal occlusion is confirmed by hysterosalpingogram (HSG) at 3 months (ACOG Committee Opinion #485). Although there are small, short-term studies of method effectiveness of hysteroscopic sterilization [48], large, prospective long-term studies are not available and are needed to better describe the safety, effectiveness and other long-term sequelae of hysteroscopic sterilization. Additionally, currently available studies use different definitions of failure (e.g., pregnancies occurring after successful placement, pregnancies occurring after HSG confirmation), making it difficult to compare studies and to calculate overall failure rates. Standard definitions of sterilization failures should be developed and should address the issue that women may not return for their confirmatory HSG and may therefore be at high risk for pregnancy despite having undergone a sterilization procedure. Prospective data from large hysteroscopic studies are also needed to make meaningful comparisons with failure rates from laparoscopic and abdominal approaches. Additionally, although there are some limited data documenting similar rates of successful placement with less vs. more experienced clinicians [49], larger prospective studies are needed to better evaluate potential “learning curves” with hysteroscopic approaches.

Given the CREST study as a model for a prospective study design to address this research gap, perhaps the greatest challenges are those inherent in large prospective multisite study designs, including the need to ensure a sufficient sample to provide adequate power for measures of effect during follow-up and the need for objective monitoring of study procedures to ensure adherence to methodology across sites. Studies involving long-term follow-up also need to take into account factors that vary over time and could affect the outcome of interest. For example, the CREST study was originally designed for women to serve as their own control [50], but given that menstrual function changes as women age, the study later began enrollment of non-sterilized women whose partners were vasectomized to serve as a comparison group, thereby allowing analyses to assess the effects of sterilization independently from the effects of aging [42]. Finally, randomization to sterilization method raises ethical and feasibility issues. Studies enrolling participants choosing a sterilization method need to match the groups being compared with respect to other factors that may affect the outcome of interest, and to otherwise capture data that would allow adequate adjustment for such factors in analysis to reduce the effects of potential biases.

5. Conclusion

We have discussed only three of several identified gaps in research that need to be addressed to provide further clarity regarding common questions of providers and women on contraceptive management and use in the United States; additional research gaps are shown in Table 1. While the aim of this paper is to present gaps in research that are directly relevant to the US SPR, other research gaps were discussed at the October 2011 expert meeting that are critically important and also deserve noting here, including the need for further research on selected safety and effectiveness issues in subgroups of the US population. Specifically, more research is needed to compile evidence of safety and effectiveness, and provider attitudes and practices, regarding contraception for obese women, including progestin-only and combined OCPs, implants, emergency contraceptive pills and IUDs (e.g., successful placement, side effects, expulsion). Research is also needed on long-acting reversible contraceptive use among teens, including studies of continuation and reasons for discontinuation, side effects of use, IUD placement and IUD expulsion, and provider attitudes and practices. Finally, to ensure maximum accessibility and use of the US SPR by providers, there is a great need for evaluation research to assess dissemination and implementation of this guidance and to identify and implement approaches for improvement. Consideration of possible quality indicators for family planning and development of metrics for these indicators could potentially help foster use of this evidence-based guidance in standard practice.

Overall, common themes in some of the identified research gaps include the need for more studies in the United States to better inform US-based practice and the need for interventions being tested to be feasible and applicable for actual use in practice in the United States; the need for sufficient statistical power in studies, with larger comparative, prospective studies to provide more conclusive evidence; the need for studies to identify effective approaches for method-specific anticipatory counseling; and, given that a major goal is to improve method satisfaction and thereby continuation of use, which should result in a reduction of unintended pregnancies, the need for studies with long-term follow-up for assessment. The evidence on which the US SPR will be based is expected to continually evolve over time. We hope this paper facilitates research to address the gaps identified, thereby strengthening the evidence that will inform future versions of the US SPR and health practitioners who provide family planning services.

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Table 1

Research gaps identified during the development of the US SPR for Contraceptive Use by the CDC

Contraceptive pill, patch and ring usage error and method adherence
What are the most effective approaches to improve patient and provider understanding of and adherence to instructions for actions to take following dosing errors with oral contraceptive pills (missed pills), the transdermal contraceptive patch and the contraceptive ring?
When combined oral contraceptive pills are missed (i.e., ≥24 h since a pill should have been administered), what is the effect of taking the most recent missed dose on the risk of unintended pregnancy?
How does prolonged use of an individual contraceptive patch or ring, due to forgotten removal or otherwise failure to remove, impact effectiveness of the method for pregnancy prevention?
What are the most effective approaches for increasing the correct and consistent use of contraceptive pills among women who choose this method?
Management of selected issues during hormonal and intrauterine contraceptive use
What are the most effective and feasible approaches for prevention and management of bleeding irregularities among women using hormonal or intrauterine contraception?
What approaches for counseling women about possible changes in their bleeding profile with use of hormonal or intrauterine contraception are most effective for improving consistency and continuation of use?
Is method efficacy preserved with vaginal administration of combined and progestin-only contraceptive pills, or emergency contraceptive pills, as an alternative for women who experience vomiting or severe diarrhea when taking the pills orally?
Does consumption of food when taking emergency contraceptive pills reduce the risk of nausea or vomiting?
What are the advantages and disadvantages of recommendations for women using an IUD to regularly check for strings of the IUD so as to possibly identify occult expulsion or displacement?
Among IUD users who become pregnant, how can ultrasound best be used to guide IUD removal when the strings are not apparent?
Contraceptive safety, effectiveness and mechanisms of action
What are the long-term effectiveness and safety of, and patient satisfaction with, hysteroscopic sterilization?
How do hormonal contraceptives (combined hormonal contraceptive pills/patch/ring, progestin-only pills, DMPA, contraceptive implants, levonorgestrel-releasing intrauterine contraception) affect cervical mucus, and do the effects vary depending on when in the cycle the method is initiated? What subject-specific or delivery-system-specific factors influence this action?
How long after implant initiation does the contraceptive effect take place (i.e., how long is a backup method needed)?
Does implant insertion on different days of the menstrual cycle affect method continuation rates?
What is the risk of unintended pregnancy if the grace period for DMPA reinjection is extended from 2 weeks to 4 weeks, thereby allowing up to 17 weeks between injections?
Is provision of DMPA prior to 11 weeks since last injection safe?
Does an interaction between the effects of ulipristal acetate (UPA) as emergency contraception and combined hormonal or progestin-only contraceptive methods reduce the effectiveness of UPA or the hormonal contraceptives, and if so, what is the relationship with the proximity of timing of use for the methods?
Provider tools, screening practices and follow-up
In the United States, what is the accuracy of the list of criteria for how to be reasonably certain that a woman is not pregnant, and does accuracy vary by patient characteristics (i.e., age)?
Among asymptomatic women, are there differences in rates of pelvic inflammatory disease among those who are screened for sexually transmitted infections at the time of IUD insertion compared with those who are not screened?
What are the incidence and prevalence of hypertension, by weight and age, in the general population of reproductive-aged women and among women using hormonal contraception, and what are the implications for needed follow-up among hormonal contraceptive users?